American Journal of Medical Genetics 62:68–70 (1996)

Epidemiological Analysis of the Association of Congenital Diaphragmatic Hernia With Upper-Limb Deficiencies: A Primary Polytopic Developmental Field Defect

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McCredie and Reid [(1978): J Pediatr 92: 762–765] described an association of diaphragmatic hernia and upper limb deficiencies. Lerone et al. [(1992): Am J Med Genet 44:827–829] recently described a new case with this combination. We present an epidemiological study using two analytic methods with data from the Spanish Collaborative Study of Congenital Malformations (ECEMC). The results support the suggestion that the concurrence of these two congenital anomalies constitutes a polytopic primary developmental field defect.

KEY WORDS: diaphragmatic hernia, limb deficiencies, association, cervical neural crest, blastogenesis, developmental field defects, polytopic field defects, epidemiology

INTRODUCTION

McCredie and Reid [1978] first described the association of congenital diaphragmatic hernia (CDH) with severe upper-limb deficiencies (ULD) in 4 unrelated infants. These authors postulated a common pathogenesis involving early cervical neural crest development. More recently, Lerone et al. [1992] published a case presenting diaphragmatic hernia and ipsilateral thumb hypoplasia, and commented that a chance association could not completely be discarded, since only 5 cases had been described previously.

Received for publication May 22, 1995; revision received September 20, 1995.

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Here I present an epidemiological analysis of this combination of anomalies using the methods proposed by Prieto and Martínez-Frías [1996], and by Khoury et al. [1990]. Both methods control the nonspecific tendency for defects to cluster among themselves. For this analysis I used a total of 21,130 live- and stillborn malformed infants (excluding those with syndromes) registered by the Spanish Collaborative Study of Congenital Malformations (ECEMC).

MATERIALS AND METHODS

This study was based on the 21,130 malformed infants with severe and/or mild malformations and some minor anomalies, excluding syndromes detected during the first 3 days of life by the Spanish Collaborative Study of Congenital Malformations (ECEMC). The methodology of this hospital-based case-control study and surveillance system is aimed not only at the surveillance of congenital anomalies, but also at investigating both clusters of congenital malformations and the causes of congenital defects. The methodology has been published previously [Martínez-Frías, 1994; Martínez-Frías and Urioste, 1994].

Two methods are used to analyze the data. The first was described by Prieto and Martínez-Frías [1996], and the second was described by Khoury et al. [1990].

As we consider only malformed infants, to analyze the data with our method [Prieto and Martínez-Frías, 1996], only three cells on a table distributing cases by

TABLE I. Distribution of Cases by the Presence or Absence of CDH Ignoring ULD*

	With diaphragmatic hernia	Without diaphragmatic hernia
With other defects	a	b
Without other defects	c	
Total	a + c	

*a, number of infants *with* CDH plus other congenital defects; b, number of infants *without* CDH but with other congenital defects, minus the number of infants with ULD as an isolated anomaly; c, number of infants with only CDH as an isolated anomaly or with only ULD.

TABLE II. Study Population

	Isolated	In MCA patterns, excluding syndromes	Total
Diaphragmatic hernia	194	87	281
Upper-limb deficiencies	316	185	501
Diaphragmatic hernia + upper-limb deficiencies	1	8	9
Total malformed infants, excluding syndromes	17,881	3,249	21,130

the presence or absence of CDH need to be covered. Table I is as follows:

To study the association of CDH with ULD, we need to count the number of infants with ULD in the different cells. Then, the proportion of infants with ULD among the a + c, and the proportion of infants with ULD among b, once the isolated ULD cases are excluded from b, are calculated. The quotient of these two proportions gives the times the proportion of infants with ULD is higher in children with CDH (with or without other congenital defects), than in infants with other congenital defects. The association of only the two studied defects (CDH and ULD) is not analyzed because a possible identification bias towards cases with less severe forms of the two defects cannot be totally excluded, since our detection period is during the first 3 days of life. Our method, like that proposed by Khoury et al. [1990], does control the generalized and nonspecific tendency for defects to cluster among themselves.

RESULTS

Table II presents the study population by clinical presentation. Table III analyzes the studied association using the method proposed by Prieto and Martínez-Frías [1996]. As can be seen, the proportion of infants with ULD is 3.72 times higher among infants with CDH (with or without other congenital anomalies) (9/281) than among infants with congenital defects other than CDH (176/20,533), and the difference is statistically significant ($P = 0.00095$). Table IV depicts the results of the analysis, using the method proposed by Khoury et al. [1990]. The observed number of cases with the association of CDH and ULD is 4.19 times higher than expected, if the association between the two studied defects is not greater than among any two others. The difference is also statistically significant ($P < 0.01$). The results of both methods are similar in that they both indicate that the presence in the same child of CDH and ULD is a nonrandom or specific combination, controlling the generalized and nonspecific tendency for the analyzed defects to cluster with any defect.

DISCUSSION

From the cases described by McCredie and Reid [1978] and that reported by Lerone et al. [1992], it appears that the association of CDH and ULD is not coincidental. McCredie and Reid [1978] suggested that a cervical neural crest injury might be the underlying common cause for both limb and diaphragm anomalies observed in their cases. Lerone et al. [1992] commented that a chance association could not be completely discarded, since only 5 cases were described in the literature. The results of our epidemiologic study strongly support the hypothesis that the association of CDH and ULD in the same child is not coincidental, but a preferential or specific combination.

The patterns of anomalies observed in our 9 cases were: 3 infants had limb-body wall complex. One had a clinical pattern compatible with trisomy 18, but the karyotype was not performed. One had a clinical pattern compatible with Fryns syndrome, although the karyotype was not performed, and I cannot totally exclude a chromosome anomaly. One had CDH, ULD, esophageal atresia, and congenital heart defects. One had CDH, ULD, and absence of nails. One had CDH, ULD, and hemivertebrae. The last case presented an MCA pattern which included mandibular dysostosis, scoliosis, upper- and lower-limb deficiencies, pulmonary hypoplasia, and cleft palate. Apart from the 9 cases observed in infants with MCA patterns, I observed 2 more cases with this association among the group of infants with well-defined syndromes. One had trisomy 18, and the other had Fryns syndrome.

TABLE III. Analysis of Association Between CDH and ULD Using Method Proposed by Prieto and Martínez-Frías [1996]*

	Infants with MCA patterns (excluding syndromes)	
	With diaphragmatic hernia	Without diaphragmatic hernia
With other defects	87 [8]	20,533[a] [176]
Without other defects	194 [1]	
Total	281 [9]	
Analysis:	$\frac{9}{281} : \frac{176}{20,533} = 3.72; P = 0.00095$	

*Brackets denote number of cases with ULD.
[a]Total of 21,130 minus 281 with CDH and minus 316 isolated ULD.

TABLE IV. Analysis of Association Between CDH and ULD Using Method Proposed by Khoury et al. [1990]

	Number of cases		Adjusted	
	Observed (O)	Expected (E)	O/E	*P*
Diaphragmatic hernia + upper-limb reduction defects	9	2.24	4.02	<0.01

The data presented here, as well as the data from the POSSUM (Pictures of Standard Syndromes and Unrecognized Malformations) and London Dysmorphology Data Base, show that the association of CDH and ULD in the same child is observed in children with such different causes as: chromosome abnormalities; genetic or unknown-cause syndromes; MCA patterns; and teratogenic agents. There is also an isolated association in children without other congenital defects [McCredie and Reid, 1978; Lerone et al., 1992]. On the other hand, I observe evidence for this association in, at least, three large epidemiological studies on limb deficiencies [Froster-Iskenius and Baird, 1990; 1992; Evans et al., 1994]. Thus, taking into account the possible common pathogenetic mechanism (which occurs during blastogenesis), together with the causal heterogeneity observed in infants with the association of these two defects, and the epidemiologic results presented here, I consider that these findings strongly support the conclusion that the association of CDH and ULD is specific or preferential, and constitutes a primary polytopic developmental field defect (DFD). Consequently, it is not a malformative complex, as was proposed by McCredie and Reid [1978] and by Lerone et al. [1992]. What is more, the association of CDH and ULD, as a problem of blastogenetic origin [Opitz, 1993], appears more frequently in infants with MCA patterns than as an isolated primary DFD.

REFERENCES

Evans JA, Vitez M, Czeizel A (1994): Congenital abnormalities associated with limb deficiency defects: A population study based on cases from the Hungarian Congenital Malformation Registry (1975–1984). Am J Med Genet 49:52–66.

Froster-Iskenius UG, Baird PA (1990): Amelia: Incidence and associated defects in a large population. Teratology 41:23–31.

Froster-Iskenius UG, Baird PA (1992): Upper limb deficiencies and associated malformations: A population-based study. Am J Med Genet 44:767–781.

Khoury MJ, James LM, Erickson JD (1990): On the measurement and interpretation of birth defect associations in epidemiologic studies. Am J Med Genet 37:229–236.

Lerone M, Soliani M, Corea D, Romero G, Martucciello G, Silengo MC (1992): Congenital diaphragmatic hernia associated with ipsilateral upper limb reduction defects: Report of a case with thumb hypoplasia. Am J Med Genet 44:827–829.

Martínez-Frías ML (1994): Developmental field defects and associations: Epidemiological evidence of their relationship. Am J Med Genet 49:45–51.

Martínez-Frías ML, Urioste M (1994): Segmentation anomalies of the vertebrae and ribs: A developmental field defect. Epidemiologic evidence. Am J Med Genet 49:36–44.

McCredie J, Reid I (1978): Congenital diaphragmatic hernia associated with homolateral upper limb malformation. A study of possible pathogenesis in four cases. J Pediatr 92:762–765.

Opitz JM (1993): Blastogenesis and the "primary field" in human development. In Opitz JM (ed): "Blastogenesis, Normal and Abnormal." New York: Wiley-Liss, Inc., for the National Foundation—March of Dimes. BD:OAS XXIX (1):3–37.

Prieto L, Martínez-Frías ML (submitted): Epidemiological analysis of the association of only two congenital anomalies in a child: A method for adjusting nonspecific clustering. Am J Med Genet 62: 61-67.